REMARKS

Status of Claims

Claims 34, 36-38, 45-50 and 65-72 were pending in the application, and were rejected for lack of enablement commensurate in scope with the breadth of the claims.

Accordingly, in compliance with the helpful suggestions of the Examiner, and to simplify and reduce the number of issues, independent claims 34, 71 and 72 have been amended and

- are limited to ***carcinoma*** [rather than cancer and precancerous conditions], and
- specify detection and comparison of levels of polynucleotides having the nucleic acid sequence of ***SEQ ID NO:1*** in suspected test samples to those in normal samples, and in the case that a higher level is detected in said suspected test sample, diagnosing the individual as having a ***carcinoma***.

The complex formulation "contacting said sample with a probe specific for a transketolase like-1 gene nucleic acid sequence, wherein said probe has a sequence that is at least 80% identical to a part of at least 15 consecutive nucleotides of SEQ ID NO:1 or is complementary or reverse complementary to such a part and wherein said probe hybridizes under stringent conditions to SEQ ID NO: 1 but does not hybridise to an other transketolase or transketolase like sequence [and] ... detecting in said suspected cancerous biological tissue sample obtained from said individual the level of polynucleotides that hybridized" has been amended to "detecting in said suspected cancerous biological tissue sample obtained from said individual the level of polynucleotides having the nucleic acid sequence of SEQ ID NO:1" since, as disclosed in paragraphs [0090] and [0091] of the specification as published, the invention is not limited to use of hybridizing probes for detection of levels of polynucleotides, but rather:

> "the means for detection of nucleic acid molecules are known to those skilled in the art. The procedure for the detection of nucleic acids can for example be carried out by a binding reaction of the molecule to be detected to complementary nucleic acid probes, proteins with binding specificity for the nucleic acids or any other entities specifically recognizing and binding to said nucleic acids. .... Another way of detecting ... is an amplification reaction of nucleic acids, which can be carried out

> in a quantitative manner such as for example the polymerase chain reaction. ... In another preferred embodiment of the invention the detection of the level of human transketolase like-1 gene products is carried out by determining the level of expression of a protein. The determination of the human transketolase like-1 gene products on the protein level can for example be carried out in a reaction comprising an antibody specific for the detection of the human transketolase like-1 protein. The antibodies can be used in many different detection techniques for example in Western-blot, ELISA or immunoprecipitation.

Further, the list of samples of step (b) of claim 72 is amended to include samples listed in paragraph [0083] of the specification as published.

Withdrawn claims are canceled.

Claim 38 is amended to provide antecedent basis for claim 49.

Claims 37 and 65-69 are newly canceled.

New dependent claim 73 is added tailored to the Examiner's indication on page 3 of subject matter for which the specification is enabling.

Accordingly, claims 34, 36, 38, 45-50, and 70-73 are now pending in the application.

Applicants have not increased the total number of claims, and appreciate that the entry of claim amendments after a final rejection is discretionary with the Examiner. However, it is respectfully submitted that each claim amendment is directly responsive to the Examiner's indications regarding the enablement issue. Thus, entry of the amendments is believed not to raise new issues or require further search.

Entry and allowance are respectfully requested.

Claim Rejections - 35 USC § 112

According to the Examiner, Claims 34, 36-38, 45-50, and 65-72 are rejected under 35 U.S.C. §112, first paragraph, because the specification is only enabling for

- an *in vitro* method for detecting carcinoma tissue in an individual (not any cancer, and not precancerous conditions)
- comprising detecting in a tissue sample obtained from said individual the level of polynucleotides comprising SEQ ID NO:1 and comparing said level to the level of

polynucleotides comprising SEQ ID NO:1 in a corresponding control tissue sample from a healthy subject,

- wherein a higher level of polynucleotides comprising SEQ ID NO:1 in the tissue sample from the individual as compared to said control tissue sample indicates that the tissue sample from the individual comprises carcinoma tissue.

In response, Applicants have amended claims 34, 71 and 72 and added new claim 73 directed to the subject matter indicated to be enabled, and respectfully request indication of allowability of these claims.

Applicants respectfully traverse the rejection of the subject matter of the remaining claims, in view of the amendments to the claims.

Enablement cancers vs. carcinoma

The Examiner finds the specification does not reasonably provide enablement for an *in vitro* method for detecting just any cancer.

Applicants respectfully submit that on page 19, lines 4-23 of WO 03/089667 it is explicitly written, that it was already known in the art that "*..the thiamine intake of cancer patients has direct consequences for the growth rate of tumors with an overexpression of the transketolase like-1 gene. ... Clinical and experimental data demonstrate increased thiamine utilization of human tumors and its interference with experimental chemotherapy. ... Antithiamine compounds significantly inhibit nucleic acid synthesis and tumor cell proliferation in vitro and in vivo in several tumor models. The medical literature reveals little information regarding the role of the thiamine dependent transketolase reaction in tumor cell ribose production, which is a central process in de novo nucleic acid synthesis and the salvage pathways for purines.*" Since the correlation between thiamin intake and cancer per se (i.e. any cancer species) was already known, the skilled artisan who studies the present patent application with the general statements concerning all known cancer species and the specific description of colon cancer, lung cancer and cancer of pancreas in examples 1-3, is learning, that the use of a TKT-L1 binding agent obviously is suitable to detect colon cancer, lung cancer and

cancer of pancreas, and predictable is suitable also to detect any other cancer species, at least those from which it was already known that they are associated with an increased thiamine utilization.

Third party evidence that the claimed methods are equally applicable to nearly all so-far known carcinomas and also other, non-carcinoma types of cancer could be found in Exhibits 1-11 filed September 13, 2007. More specifically, Exhibit 1, (Langbein et al., British Journal of Cancer (2006) 94, 578-584), discloses that the overexpression of TKTL-1 also occurs in bladder-, breast-, thyroid-, prostate-, pancreas-, ovarian-, cervix-, rectal-, and kidney carcinomas as well as in melanoma and glioblastoma (*see esp.* page 580. right column, second paragraph). The cancers mentioned in Exhibit 1 belong to the most aggressive cancer types of all. Exhibit 1 as well as Exhibit 2 (Földi et al.), Exhibit 6 (Staiger et al.), Exhibit 7 (Völker et al.), Exhibit 8 (Langbein et al.), Exhibit 9 (Völker et al.), Exhibit 10 (Kayser et al.) and Exhibit 11 (Krockenberger et al) demonstrate for several different types of tissues that in cases of overexpression of TKTL-1 in abnormal proliferating cells an aggressive tumor is present, forming or capable of forming metastasis and potentially resulting in the death of the respective individual.

The specification is enabling to those of ordinary skill pursuant to the standards provided in MPEP 2163.02 and *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989); *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)); *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 969-70, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002); *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980); *In re Brana*, 51 F.3d 1560, 34 USPQ 1436 (Fed. Cir. 1995); *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980); *In re Malachowski*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1976); *In re Gaubert*, 530 F.2d 1402, 189 USPQ 432 (CCPA 1975); *In re Gazave*, 379 F.2d 973, 154 USPQ 92 (CCPA 1967); *In re*

Hartop, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 130 USPQ 215 (CCPA 1961); *Ex parte Maas*, 9 USPQ2d 1746 (Bd. Pat. App. & Inter. 1987); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991). *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)); *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991); *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); *Enzo Biochem*, 323 F.3d at 963, 63 USPQ2d at 1613.

Nevertheless, in order to expedite examination, Applicants have limited the claims to carcinoma, without surrendering the right to pursue broader subject matter in a continuation or divisional application.

Accordingly, the rejection is rendered moot.

The term "precancer" has an art accepted, well recognized, definite meaning

The Examiner finds the specification does not reasonably provide enablement for an *in vitro* method for detecting just any precancerous condition, and objects to the claims for including methods wherein just any precancerous condition is detected. Because normal tissue is "precancerous", the claims encompass contradictory methods wherein higher levels of detected polynucleotides are indicative of cancer and normal tissue.

Applicants respectfully submit that the term "precancer" has an art accepted, well recognized, definite meaning. See the published results of a conference convened on this very topic, J. Berman, et al ***Precancer****: A conceptual working definition: Results of a Consensus Conference,* Cancer Detection and Prevention, Volume 30, Issue 5, Pages 387-394 (2006) (http://www.cancerepidemiology.net/). Precancers are lesions that precede the appearance of invasive cancers. The successful prevention or treatment of precancers has the potential to eliminate deaths due to cancer.

Nevertheless, in order to expedite examination, Applicants have limited the claims to carcinoma, without surrendering the right to pursue broader subject matter in a continuation or divisional application.

Accordingly, the rejection is rendered moot.

"detecting the level of polynucleotides comprising SEQ ID NO:1" vs. "contacting said sample with a probe specific for a transketolase like-1 gene having the nucleic acid sequence of SEQ ID NO:1 and detecting the level of polynucleotides that hybridized"

In view of the Examiner's indication of the subject matter for which the specification is enabling, Applicants amend claims 34, 71 and 72 and have add claim 73.

The rejection is thus rendered moot.

Predictability

According to the Examiner, this invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology".

In response, the claims have been limited to be commensurate in scope with the determination of enablement, thus, this ground of rejection is rendered moot.

Examiner's Response to Applicant's Reply

The Examiner notes that, in the Reply of 3/9/09, Applicant states that the claimed invention relates to a link between overexpression of TKT-L1 and disorders characterized by *abnormal cell proliferation.*

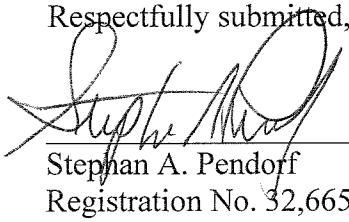
In response, Applicants submit that claims 34, 71 and 72 as amended are now limited to diagnosis of carcinoma by the detection of levels of polynucleotides having the nucleic acid sequence of SEQ ID NO:1, thus previous grounds of rejection and arguments in support of broader claims are rendered moot.

In view of the foregoing, reconsideration and withdrawal of all rejections and early issuance of the Notice of Allowance is respectfully solicited.

If the Examiner believes that a telephone conversation with the Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at the telephone number shown below.

The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 16-0877.

Respectfully submitted,



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